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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/717,450	11/20/2000	Lisa Ann Neuhold	0630/D532US1	5417

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EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/717,450	NEUHOLD ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2002 and 10 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's arguments filed 4-30-02, paper number 9, have been fully considered but they are not persuasive. Claims 28, 30-32, 35-38, 40-46, 48, 49, 51-54 were amended in paper number 9. In response to paper number 9, the Examiner sent a non-compliance letter on 10-10-02, paper number 10. Applicants filed a response on 1-10-03, paper number 11. The request to transfer the sequence listing from the parent application was received in paper number 11. Claims 28-54 were canceled in paper number 11. Claims 55-96 were added in paper number 11 and are under consideration in the instant office action. Paper number 11 included support for the amendments but did not include any additional arguments. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The IDS filed 2-28-01 remains improper because the citations are incomplete for reasons of record. For publication purposes, proper citations are required. The citation, DE 19501032A1, remains not considered because a translation has not been provided in this application or the parent application.

Claim Rejections - 35 USC § 112 – written description

Claims 55-69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention for reasons of record.

The phrase "chondrocyte tissue-specific promoter" lacks written description for reasons of record because the specification does not disclose any promoters that cause expression exclusively in chondrocytes. For example, the specification and the art do not teach the Type II collagen promoter is expressed only in chondrocytes or teach the expression pattern of Type II collagen promoter in non-chondrocytes. Without such guidance, the specification does not provide adequate written description for any "chondrocyte tissue-specific promoter" as claimed. An adequate written description of a "chondrocyte tissue-specific promoter" requires more than a mere statement that it is part of the invention. What is required is a description of the promoter itself. It is not sufficient to define a promoter as being "chondrocyte-specific" because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of promoters that function only in chondrocytes or only in a specific type of chondrocyte. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, the limitation of promoters that are "chondrocyte-specific" without defining species within the genus is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Applicants argue the phrase "chondrocyte tissue-specific promoter" is described on pg 37, line 1, pg 6, line 4, and pg 13, line 3. Applicants' argument is not persuasive. Pg 36, line 22, contemplates a "fusion protein operably linked to a joint-specific (type II collagen) promoter as well as a reporter gene suitable

for assessing the tissue-specific expression conferred by the type II promoter." Thus, according to pg 36, line 22, the Type II collagen promoter is a "joint-specific promoter;" not a "chondrocyte-specific promoter" as claimed. Pg 6, line 4, states, "In preferred embodiments, the recombinant MDE-encoding genes are selectively expressed in articular chondrocytes...." Pg 13, line 3, states "MMP activity is selectively expressed in joint tissues, most preferably in articular chondrocytes." "Specific" is defined as "constituting or falling into a specifiable category...; restricted to a particular individual, situation, relation, or effect..." "Selectively" is defined as "highly specific in activity or effect." Thus, chondrocyte-specific expression is limited to expression in chondrocytes while selectively expressing in chondrocytes is not limited to specific expression and merely requires "highly specific" expression in chondrocytes. In addition, articular chondrocytes are a narrower species of the genus chondrocytes. Therefore, pg 6, line 4, and pg 13, line 3, do not contemplate the genus of "chondrocyte-specific promoters."

Applicants argue the phrase "chondrocyte tissue-specific promoter" is described on pg 15, line 19, through pg 16, line 6. Applicants' argument is not persuasive. The citation describes "selective expression in joints" (pg 15, line 20) and "joint-specific expression" (pg 15, line 20) as

> "expression that is greater than in other cells; typically, the level of expression in non-joint tissues is less than 10% of the level of expression in joints. Preferably, expression in non-joints is undetectable. Useful promoter sequences that confer joint-specific expression on a sequence to which they are operably linked include without limitation sequences derived from the collagen type II promoter."

Thus, applicants consider the collagen type II promoter a "joint-specific" promoter and not a "chondrocyte-specific promoter" as claimed. The citation does not describe the genus of "chondrocyte-specific promoters."

Applicants point to pg 41-45 (Example 5 and 6) and state the phenotypic characteristics of the transgenic mouse of the invention are described and support the phrase "chondrocyte tissue-specific promoter". Applicants' argument is not persuasive. Examples 5 and 6 do not teach the expression pattern of MMP in the tissues of the mouse, specifically that expression was limited to or preferentially expressed in chondrocytes. It cannot be determined what tissues in the joint expressed the protein or that expression was specific to chondrocytes.

Overall, the specification does not describe the collagen type II promoter is a "chondrocyte tissue-specific promoter." If applicants were to show that collagen type II promoter is a "chondrocyte tissue-specific promoter," then the specification does not describe any other promoters that are "chondrocyte-specific." Therefore, the specification does not provide adequate written description for the species of promoters in the genus of "chondrocyte tissue-specific promoters."

The phrase "chondrocyte tissue-specific promoter" remains new matter. While the specification mentions obtaining selective expression of MMP in join tissues, preferably in articular chondrocytes (page 6, line 4; page 13, line 3), such expression does not support the genus of "chondrocyte tissue-specific promoter" because it is not "specific" to chondrocytes. The specification teaches assessing the tissue-specific expression of the Type II collagen promoter (page 37, line 1), but does not teach Type II collagen promoter <u>is</u> specific to any tissue, specifically

chondrocytes. Therefore, the specification does not support the genus of "chondrocyte tissue-specific promoter."

Applicants' arguments are addressed above in the written description rejection.

Claim Rejections - 35 USC § 112 – enablement

Claims 54-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises: a) a nucleotide sequence encoding a constitutively active, human MMP that cleaves Type II collagen, wherein the nucleotide sequence is operatively linked to a regulatable promoter; and b) a nucleotide sequence encoding a transcription activator or repressor protein operatively linked to a Type II collagen promoter, wherein expression of the metalloproteinase is capable of being repressed in the mouse until adulthood, and wherein the metalloproteinase is capable of being expressed in the mouse during adulthood to a level sufficient to cause degradation of type II collagen, does not reasonably provide enablement for any non-human mammal, any "matrix degrading enzyme that degrades an Type II collagen," or any "chondrocyte tissue-specific promoter." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The claims are directed toward a transgenic non-human mammal whose genome comprises DNA encoding an MMP that cleaves Type II collagen in a regulatable system capable of Type II collagen degradation during adulthood, methods of degrading Type II collagen in such a mammal, and methods of evaluating compounds using such a mammal.

The state of the art at the time of filing was that it was unpredictable how to obtain the phenotype of interest in transgenics. The species-specific requirements for transgene design are not clearly understood. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins of record (1990, Nature, Vol. 344, pg 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer of record (1990, Cell, Vol. 63, pg 1099-1112) described spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, EMBO, Vol. 8, pg 4065-4072; Taurog, 1988, J. Immunol., Vol. 141, pg 4020-4023, both of record) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Thus, the combination of elements (protein, promoter, species of protein, and species of transgenic) required to obtain a desired phenotype were not within the realm of routine experimentation at the time of filing. The art at the time of filing also taught that attempts to engineer transgenic animals expressing MMP, e.g. MMP1 and stromelysin have not resulted in joint degeneration (pg 4, line 15, of the instant specification). As such the combination of protein, promoter, and species of transgenic required to degrade type II collagen in transgenics were unpredictable at the time the invention was made.

Not only is the difference in transgenic mice and rats unpredictable for reasons stated above, the art at the time of filing was such that a number of

significant limitation regarding the production of non-mouse transgenic animals existed. Wall of record (1996, Theriogenology, Vol. 45, pg 57-68) disclosed the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Ebert of record (1988, Mol. Endocrinology, Vol. 2, pages 277-283) taught a transgene encoding the human somatotropin gene operably linked to the mouse metallothionein promoter caused different phenotypes in transgenic pigs and mice (pg 277, col. 2, lines 17-27). Overbeek of record (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pg 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (pg 96, last para). Mullins of record (1996, J. Clin. Invest., Vol. 98, pg S37-S40) taught that non-mouse ES cells capable of providing germline chimeras were not available (pg S38, col. 1, 1st para). Therefore, it was unpredictable at the time of filing what gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, site of integration, method used and phenotype obtained were required to make a transgenic non-human mammal of interest. The art at the time of filing did not teach any transgenic non-human mammal expressing an MMP that degrades Type II collagen or any other matrix-degrading enzyme.

The specification teaches making a transgenic mouse whose genome comprises: a) a nucleotide sequence encoding a constitutively active, human MMP that cleaves Type II collagen, wherein the nucleotide sequence is operatively linked to a regulatable promoter; and b) a nucleotide sequence encoding a transcription activator or repressor protein operatively linked to a

Type II collagen promoter, wherein expression of the metalloproteinase is capable of being repressed in the mouse until adulthood, and wherein the metalloproteinase is capable of being expressed in the mouse during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the mouse. Expression is controlled by the administration/withdrawal of tetracycline or other regulatory compound.

Enablement of any "metalloproteinase that cleaves Type II collagen"

Claims 55-57, 60-77, 80-96 do not require the metalloproteinase (MMP) is constitutively active. Claims 58 and 78 require the MMP is constitutively active. Claims 59 and 79 require the MMP is SEQ ID NO:1 or 21, which are constitutively active. The specification teaches MMPs that degrade Type II collagen (page 2-3). The specification teaches circumventing the need for proteolytic processing of MMPs expressed in transgenics during adulthood using enzyme variants that are enzymatically active even when uncleaved (i.e. "constitutively active," pg 11, line 22 through pg 12, line 12). The specification does not teach how to control proteolytic processing or provide adequate correlation between constitutively active and non-constitutively active human MMPs that degrade Type II collagen. Therefore, using constitutively active MMPs is essential for degrading Type II collagen in the transgenic claimed. It would have required one of skill in the art undue experimentation to determine how to control proteolytic processing so the MMP was properly cleaved, enzymatically active and capable of degrading Type II collagen. Therefore, the MMP in the claims should be constitutively active as in claims 58 and 78.

Applicants have not argued this rejection. The response filed 4-30-02 states the claims are limited to "constitutively active" enzyme (para. bridging pg 24-25); however, the limitation was deleted in the response filed 1-10-03.

Enablement of any "chondrocyte-specific promoter"

Claims 55-64, 66-79, 81-96 are generic to any "chondrocyte-specific promoter" while claims 65 and 80 are limited to the type II collagen promoter. The specification teaches the Type II collagen promoter and mentions obtaining selective expression of MMP in join tissues, preferably in articular chondrocytes. The specification does not teach any promoters related to chondrocytes, any chondrocyte-specific promoters or any means of obtaining expression preferably in the articular chondrocytes. While some promoters related to chondrocytes were known in the art, the art and the specification do not teach using such promoters in transgenics or that expression was limited to chondrocytes. In addition, a number of promoters were known in the art that functioned in transgenics; however, they were not chondrocyte-specific, or used to degrade Type II collagen. Therefore, the specification does not enable using any chondrocyte-specific promoter as broadly claimed.

In the response filed 4-30-02, applicants argue the specification enables "joint-specific promoters" (pg 25, 1st para.); however, the limitation of "joint-specific promoter" was changed to "chondrocyte-specific promoter" in the response filed 1-10-03. Applicants point to para. 5 of the 2nd declaration by Dr. Neuhold which states the promoter used to achieve tissue specific expression does not make any difference. Applicants' arguments are not persuasive. Niemann (1997, Transg. Res. Vol. 7, pg 73-75) taught transgenic pigs made with different promoters regulated in expression of a growth hormone caused various

phenotypes - one deleterious to the pig, the other compatible with pig health (pg 73, col. 2, parag. 2, line 12 to page 74, col. 1, line 4). The specification does not correlate the Type II collagen promoter to any other promoter that provides the same level of expression or tissue specificity as Type II collagen promoter. Without such guidance, it would require one of skill undue experimentation to determine other "chondrocyte-specific promoters" that provided the same tissue specificity as Type II collagen promoter, the same levels of expression as Type II collagen promoter, or the phenotype of interest.

Applicants point to US patents that claim using "mammary-gland specific promoter" and "cardiac-specific regulatory region" in transgenics (pg 26 of the response filed 4-30-03). Applicants' argument is not persuasive as each application is examined on its own merits.

Enablement of any "transgenic non-human mammal"

Claims 55-63, 67-71, 75-91, 93-96 are generic to any transgenic non-human mammal while claims 64-66 are limited to a transgenic rat. Given the unpredictability of phenotypes between mice and rats taken with the unpredictability regarding obtaining transgenics other than mice, the unpredictability regarding the parameters required to obtain a phenotype of interest in transgenics and the lack of guidance provided in the specification regarding how to obtain transgenics other than mice and the lack of guidance provided in the specification regarding how to obtain Type II collagen degradation in mammals other than mice and the lack of correlation in the specification regarding how to obtain the phenotype found in mice in other mammalian species, the specification does not enable making any transgenic non-human mammal capable of degrading Type II collagen as claimed other than mice.

Applicants argue that transgenic mammals had been made in the art as of 1996. The second declaration of Dr. Neuhold (Exhibit 5, para. 9) states generating transgenic animals having the desired feature was routine at the time of filing. The declaration refers to Bradley (1996, Nature Genetics, Vol. 14, pg 121) who states

> "For almost 15 years the methods for making transgenic mammals have remained virtually unchanged, consisting of the injection of naked DNA into the pronucleus of a fertilized egg. The technique is so reliable that the technical shortcomings can readily be circumvented by producing an excess of experimental material so that animals with the desired experimental outcome can be selected from a collection of founder mice[1]."
>
> 1. Palmiter (1985, Cell, Vol. 41, pg343-345).

Dr. Neuhold concludes para. 9 by stating that as of 1996, creation of transgenic mammals required no more than ordinary technical effects (para. 9).

Applicants' arguments are not persuasive.

Bradley (1996) taught animals with the "desired experimental outcome" can be selected from a collection of founder mice. In context, Bradley (1996) merely discusses the ability to screen a collection of founder transgenics to determine founders that carried the transgene of interest. Bradley did not teach screening founder mice predictably resulted in identifying animals with the desired phenotype. Bradley did not teach how to make any mammals other than mice (see the citation at the end of the first sentence of Bradley, i.e. Palmiter, which only taught making transgenic mice). Bradley did not teach making non-mouse transgenics was routine. Bradley did not teach the phenotype obtained in transgenic mice predictably occurs in other mammals. The art taught

phenotypes in mice do not occur in rats using the same construct (Mullins (1990), Hammer (1990), Mullins (1989), Taurog (1988) all of record). Mullins of record (1996, J. Clin. Invest. Vol. 98, pg S37-S40) taught transgene constructs react very differently from one species to another (pg S38, col. 1, last para.). Mullins (1993, Hypertension, Vol. 22, pp. 630-633) taught integration of a transgene into different species of animal gave divergent phenotypes. Ebert of record (1988, Mol. Endocrinology, Vol. 2, pages 277-283) taught a transgene encoding the human somatotropin gene operably linked to the mouse metallothionein promoter caused different phenotypes in transgenic pigs and mice (page 277, column 2, lines 17-27). Wall of record (1996, Theriogenology, Vol. 45, pages 57-68) taught the physiological result of transgene expression in livestock was not predicted in transgenic mice (page 62, line 7). Therefore, the mere ability to make and screen transgenics that carry the transgene construct is not adequate for one of skill to predictably obtain the phenotype in mice in other mammalian species.

Dr. Neuhold states in para. 10 that the elements used in the mouse disclosed could be used in non-mouse species and "the only uncertainty remaining was to establish that this combination of features would cause phenotypic changes of osteoarthritis in a transgenic animal" (para. 10) which are described in the specification and could easily be screened for. Dr. Neuhold states in para. 11 that by teaching the combination of elements used to obtain the phenotype of interest in mice, there is a more than reasonable expectation of obtaining any transgenic mammal which will work better.

Applicants' arguments are not persuasive. The specification, the declaration of Dr. Neuhold and Bradley (1996) do not adequately correlate the elements used in the disclosed mouse to other mammals such that the phenotype obtained in mice could be obtained in other mammals. The specification does not teach the level of expression of MMP and expression of the regulatory protein obtained in mice would be the same in other mammals using the same construct. The specification does not teach the Type II collagen promoter causes the same level of protein expression in mice and other mammals. The specification does not teach MMP degrades collagen to the same extent in mice and other mammals. The specification does not teach MMP causes the same level of Type II collagen degradation cause the symptoms claimed in mice and other mammals. The specification does not teach the level of regulatory protein expressed that regulates MMP expression in mice is the same level required in other species. Without such guidance, taken with the unpredictability in the art, one of skill could not predict whether the phenotype in mice would occur in other species. Mere screening for a phenotype of interest would not allow one of skill in the art to predict whether the phenotype would occur in species other than mice.

Applicants argue mice and rats are closely genetically related; therefore, an example of a transgenic mouse having the phenotype claimed is adequate to enable a rat having the phenotype claimed (pg 22 of the response filed 4-30-02). Applicants' argument is not persuasive. The genetic diversity of mice and rats adds to the unpredictability of whether the phenotype of interest would occur in

rats. Cameron (1997, Molec. Biol., Vol. 7, pg 253-265) taught expression of a transgene was unpredictable because of the insertion site of the transgene into the genome and the surrounding genetic background. Predictable levels of expression are not achieved because of the complete absence of expression or leaky expression in non-target tissues (pg 256, para. bridging col. 1-2). Factors causing variable expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (pg 256, col. 2, lines 3-9). These factors are copy number independent and integration site dependent, emphasizing the role the genetic background and site of integration in the level of expression of the transgene (pg 256, lines 10-13). Since mice and rats having increased genetic diversity, the unpredictability of whether the phenotype obtained in mice would occur in rats is increased.

Applicants argue Mullins of record supports applicants position and does not establish the unpredictability in the art as asserted by the examiner. Applicants' argument is not persuasive. Applicants' argument does not address the basis of the rejection, which is the lack of ability for one of skill to predictably obtain the phenotype of interest in non-mouse mammals based on the phenotype obtained in mice. Mullins taught ES cell technology was limited to mice and not in any other species. Mullins does not teach how to predictably obtain a phenotype of interest in non-mice. Therefore, Mullins helps to establish the lack of correlation between making mice and other transgenic mammals.

Claim Rejections - 35 USC § 112 – indefiniteness

Claims 90-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claim 90 is indefinite because the scope of "non-human mammal" and "transgenic mammal" on lines 2 and 4, respectively, is not commensurate.

Step (a) in claims 90-96 is indefinite because it is unclear if the step is limited to administering the compound to the mammal resulting in expression of the MMP or to administering the compound to a mammal in which expression of the MMP has been activated. If MMP activation is required in the mammal used in step (a), it is unclear if Type II collagen has occurred.

The phrase "the extent of..." in step (b) of claims 90-96 is indefinite because it lacks antecedent basis. Step (b) is confusing because the phenotypes listed may not occur and are not required in step (a) or in the parent claims. Overall, it is unclear when the compound is administered to the mammal relative to administering the regulatory compound, obtaining MMP expression and degrading Type II collagen in the joints.

Step (c) of claims 90-96 remains indefinite because it does not clearly describe the control mammal. What are the metes and bounds of the phenotype of the control mammal? Is it transgenic? Step (c) is indefinite because the phrase "any less extensive development in the nature or extent of, or any difference in the time required for the loss of proteoglycan... ...to develop" is unclear. It is unclear how to determine the "difference" in a phenotypic "change". It is unclear whether the test requires comparing the development of the phenotypes listed in both test and control mammals, comparing a characteristic of osteoarthritis over period of time in the test and control mammals, or

comparing a characteristic of osteoarthritis at a specific time in the test and control mammals. Finally, the test requires determining a change in phenotype; however, the claim states any "change" indicates the composition may counteract osteoarthritis. The composition may in fact change the mammal by increasing osteoarthritis; therefore, a mere change in phenotype does not indicate the composition counteracts osteoarthritis as claimed.

Applicants' arguments regarding previous claims 52-54, directed to a similar invention (pg 28, last two lines, in the response filed 4-30-03), do not apply to claims 90-96 as amended in the response filed 1-10-03.

The claims are free of the prior art of record.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will

the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER